# Armed Forces College of Medicine

# AFCM

# Wrap up Biochemistry GIT Module

# The active form of riboflavin is:

a) FAD
b) NAD
c) FMN
d) a & b
e) a & c

# Functions of Riboflavin vitamin (B2)

**Active forms:** flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) which acts as hydrogen carrier *in oxidation-reduction* reactions

## Reactions catalyzed by FAD

For example:

1- Succinate dehydrogenase

2- Glycine oxidase

3- Alpha keto acids dehydrogenase complex

## Reactions catalyzed by FMN

For example:

1- L-amino acid oxidase

2- NADH dehydrogenase complex (respiratory chain)

# Case

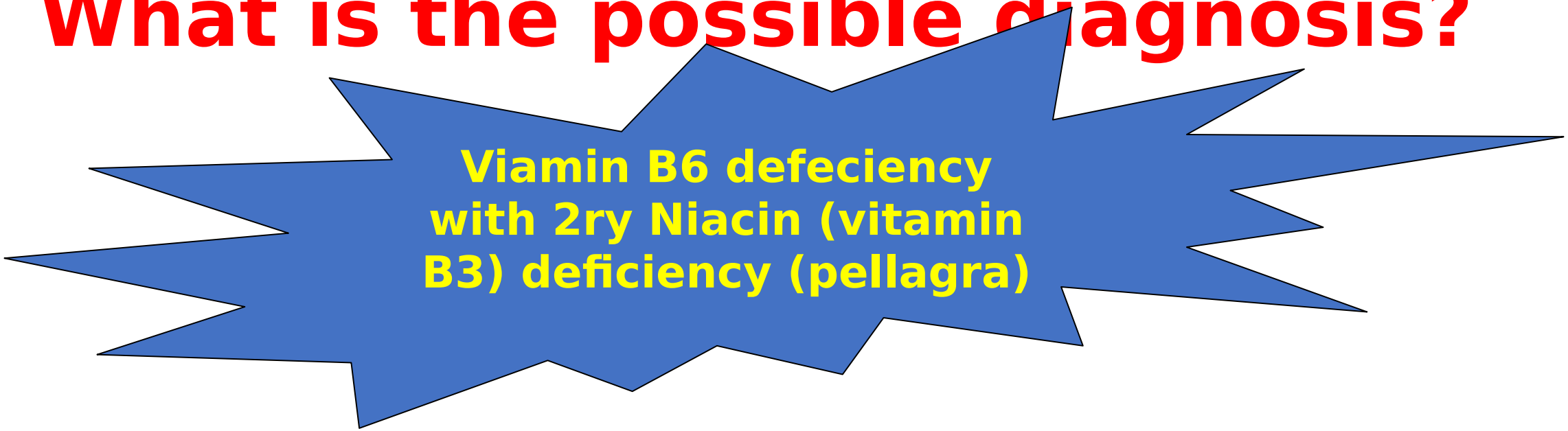
- A 45-year-old male was admitted after being found lying naked in the street talking to himself
- On admission, he had severe pallor.
- On physical examination ,his hands and forearms were covered with erythematous scaly lesions. He had persistent diarrhea without any evidence of GIT infection.
- Mental status examination on admission found that the patient was conscious but unable to answer questions correctly. Based on retrospective history from his family members, he has a history of alcohol abuse, history of seizure with no history of psychiatric disorder.

# Case

- CBC revealed sideroblastic anemia with normal iron profile.
- Decreased plasma PLP level
- A 24-hour urine test found decreased levels of N-methylnicotinamide (<0.5 mg) and together with the clinical symptoms, a diagnosis of niacin deficiency (i.e., pellagra) was made.
- The patient subsequently returned to the psychiatric hospital and was treated with high-dose niacin acid, vitamins B complex. Thirty-five days after the initial admission his cognitive functioning improved, the skin color of his face and forearms lightened, the peeling of his skin lessened.

Sideroblastic Anemia

# What is the possible diagnosis?

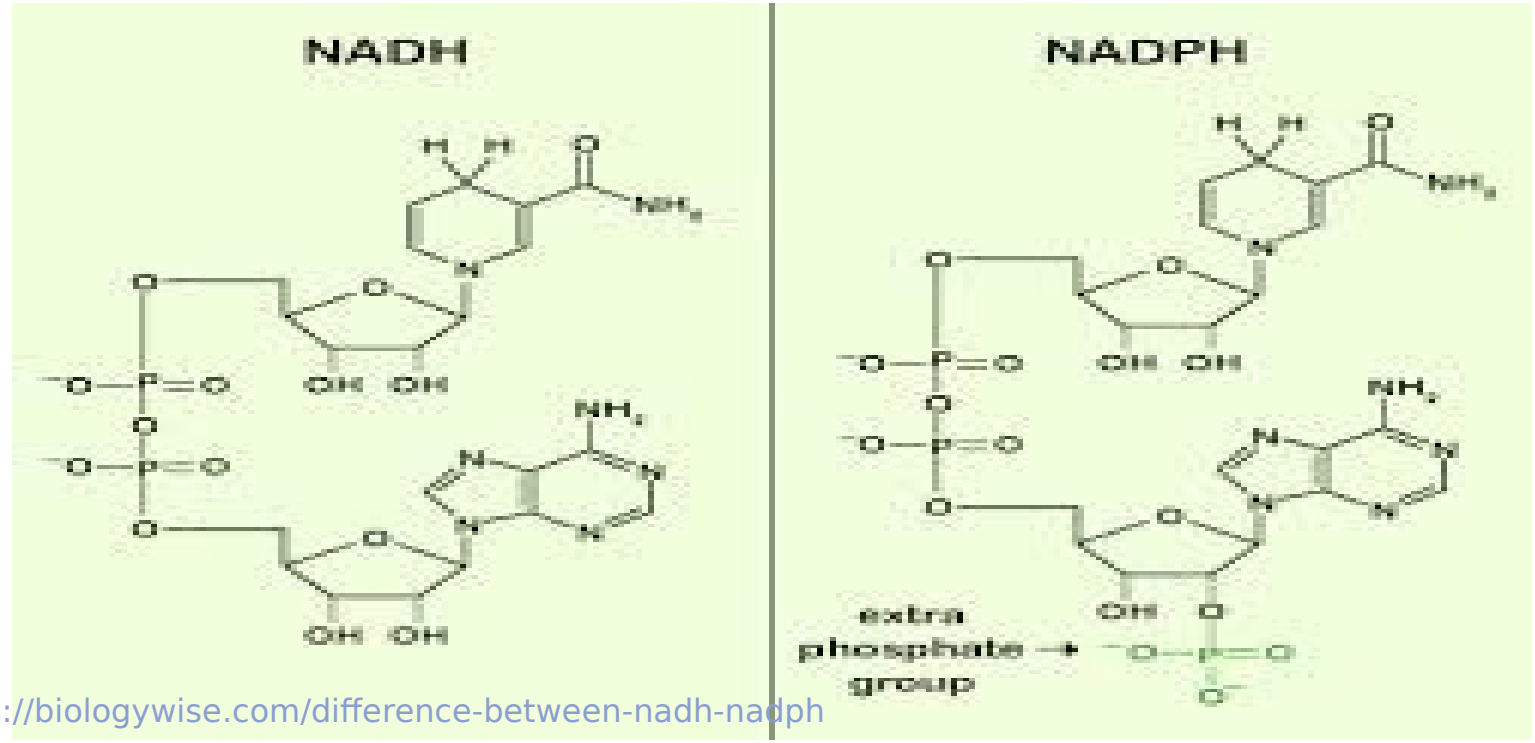



- Alcohol abuse (malnutrition, vitamin deficiency)
- Dementia
- Dermatitis in sun exposed areas
- Diarrhea

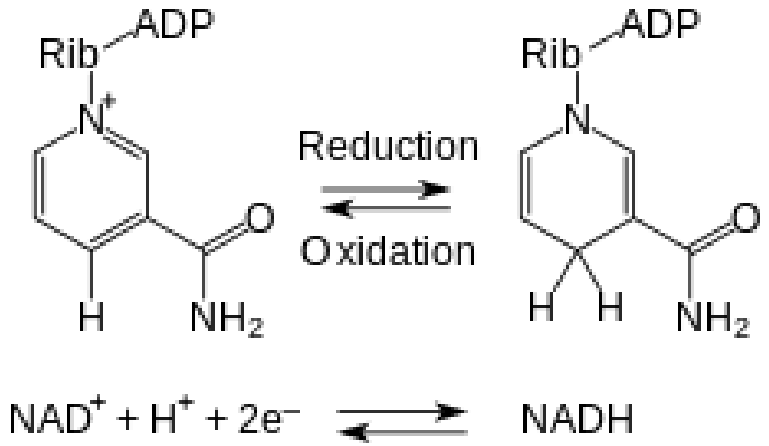
# Niacin (nicotinic acid ) ($B_3$)
# Pellagra Preventive Factor (PPF)


**Niacin is not strictly a vitamin since it can be synthesized from tryptophan (needs vitamin B6)**

**It is converted in the body into 2 hydrogen carriers** (nicotinamide adenine dinucleotide **(NAD) &** nicotinamide adenine dinucleotide phosphate **(NADP)**




https://biologywise.com/difference-between-nadh-nadph




https://en.wikipedia.org/wiki/Nicotinamide_adenine_dinucleotide

## NAD dependant enzymes

1. Glyceraldehydes 3-phosphate dehydrogenase
2. Lactate dehydrogenase
3. Pyruvate dehydrogenase complex
4. Mitochondrial isocitrate dehydrogenase.

## NADP dependant enzymes

HMP

1. Glucose 6–phosphate dehydrogenase
2. 6-phosphogluconate dehydrogenase
3. Malic enzyme
4. Cytosolic isocitrate dehydrogenase
5. Glutathione reductase.

**NADH generated is oxidized in the respiratory chain to generate 3ATP.**

# Niacin Deficiency (Pellagra)

## Causes:

i. **Decrease Intake of Tryptophan & Niacin**

ii. **Vitamin $B_6$ deficiency (decreased conversion of Tryptophan to niacin)**

iii. **Caricinoid syndrome (shunting of tryptophan to serotonin synthesis )**

iv. **Hartnup's disease (decreased absorption of tryptophan): it is a Genetic condition in which there is a defect of the membrane transport mechanism for tryptophan, resulting in large losses as a result of [illegible] failure of renal reabsor[illegible]**

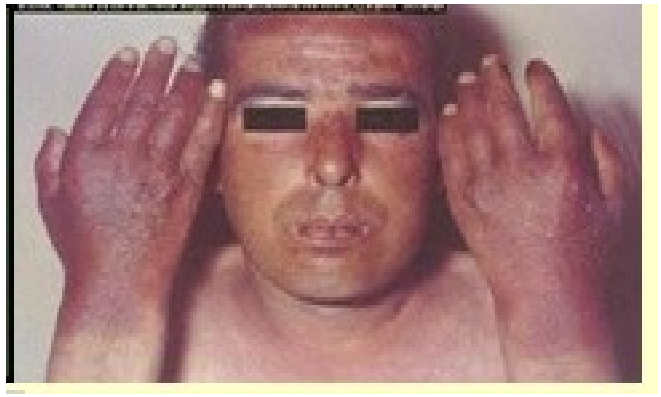
**Explain on biochemical basis pellagra manifestations in Hartnup's disease**

# Manifestations: 3Ds

**A.Dermatitis :rough scaly skin dark coloration of skin on the exposed parts of the body**

**B.Diarrhoea**

**C.Dementia: irritability, poor memory, peripheral neuritis and depression which end by dementia**



# Which of the following enzymes IS NOT NAD dependent?

a) glyceraldehyde 3-phosphate dehydrogenase

b) lactate dehydrogenase

c) Succinate dehydrogenase

d) pyruvate dehydrogenase complex

e) mitochondrial isocitrate dehydrogenase

# Oxidation of one molecule of NADH+H yields:

a)1 ATP

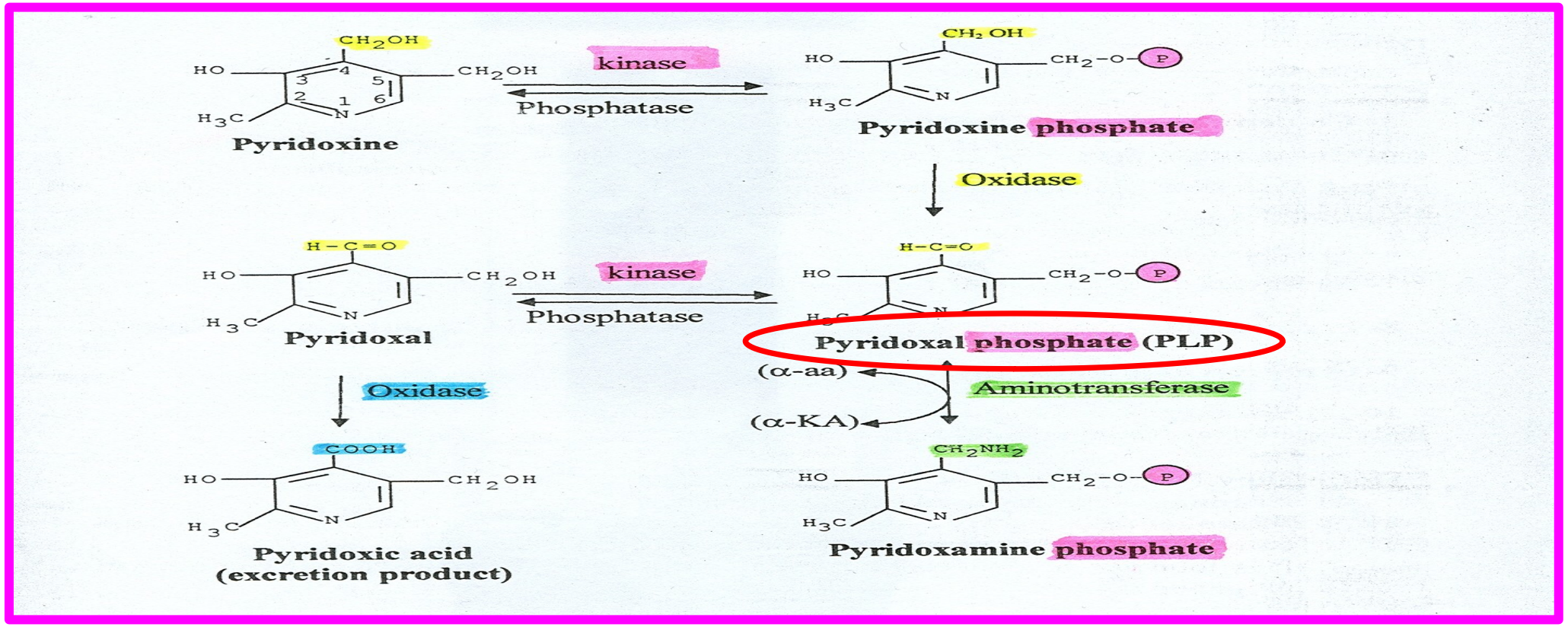
b)2 ATPs

c)3 ATPs

d)4 ATPs

# Pyridoxine vitamin (B6)


- **Active form of pyridoxine is pyridoxal phosphate (PLP).**

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# Functions of PLP

## Protein metabolism

1 absorption of amino acids and its uptake .

2- Transamination reactions e.g. ALT and AST.

3- decarboxylation reactions of amino acids

4- Methionine and cysteine metabolism

5- conversion of tryptophan to niacin.

6-Non-oxidative deamination .

## Heme synthesis

4- **ALA synthase** in heme biosynthesis. So, in B6 deficiency, anemia is common.

## Lipid metabolism

6- coenzyme in the formation of **sphingosine** from palmitoyl-CoA and serine.

## Carbohydrate metabolism

**Muscle glycogen-7 phosphorylase** has a pyridoxal phosphate at each catalytic site

# Deficiency of Vitamin $B_6$

**Causes of deficiency:**

- **Pregnancy**
- **Alcoholics**
- **Oral contraceptives & Penicillamine**
- **Tuberculous patient treated with isoniazid (explained later)**

**Manifestations**:

**1-Hypochromic anemia** due to impaired heme synthesis.

**2-Neurological manifestations** :

**I.Peripheral neuritis (stock and glove)** as PLP is involved in **sphingolipid synthesis**; so $B_6$ deficiency leads to demyelination of nerves.

**II.Convulsions,** particularly in children due to decreased formation of GABA.

**3-Pellagra like manifestations** due to decreased conversion of tryptophan to niacin.

**4-Homocysteinemia and homocystinuria**

**Explain on a biochemical causes neurological manifestation in vitamin B6 deficiency?**

**Which of the following reactions is likely to be impaired in vitamin B6 deficiency?**

a)Ornithine to citrulline

b)Histidine to Histamine

c)Glutamate to glutamine

d)Propionyl coA to methylmalonyl CoA

e)Phenylalanine to tyrosine

# Explain the likely cause of anemia in this patient.

**vitamin B6 is required for the action of ALA synthase in heme biosynthesis. So, in B6 deficiency, anemia is common.**

# Enumerate decarboxylation reactions requiring vitamin B6.

**i- Glutamate ———→ gamma amino butyric acid (GABA)**

**ii- Histidine ———→ histamine**

**iii-5- Hydroxytrytophan ———→ serotonin**

**iv- Cysteine ———→ thioethanolamine and taurine**

**v- Serine ———→ ethanolamine**

# What might be the causes of neurological manifestations in vitamin B6 deficiency?

- Peripheral neuritis as PLP is involved in sphingolipid synthesis; so $B_6$ deficiency leads to demyelination of nerves.
- Convulsions, due to decreased formation of GABA and other neurotransmitters.

# What is the link between PLP and CHO metabolism?

**PLP acts as a coenzyme for Muscle glycogen phosphorylase**

## Case study

**A 37 -years-old female suffering from neurological manifestations is referred to a neurologist by her primary care physician.**

**Laboratory investigations showed low serum ceruloplasmin, and increased free copper in urine.**

# List Biological functions of cu enumerating enzymes that need copper as a co-factor.

- Help in iron absorption in Ferric state
- Hb synthesis
- Bone formation
- Nervous tissue function

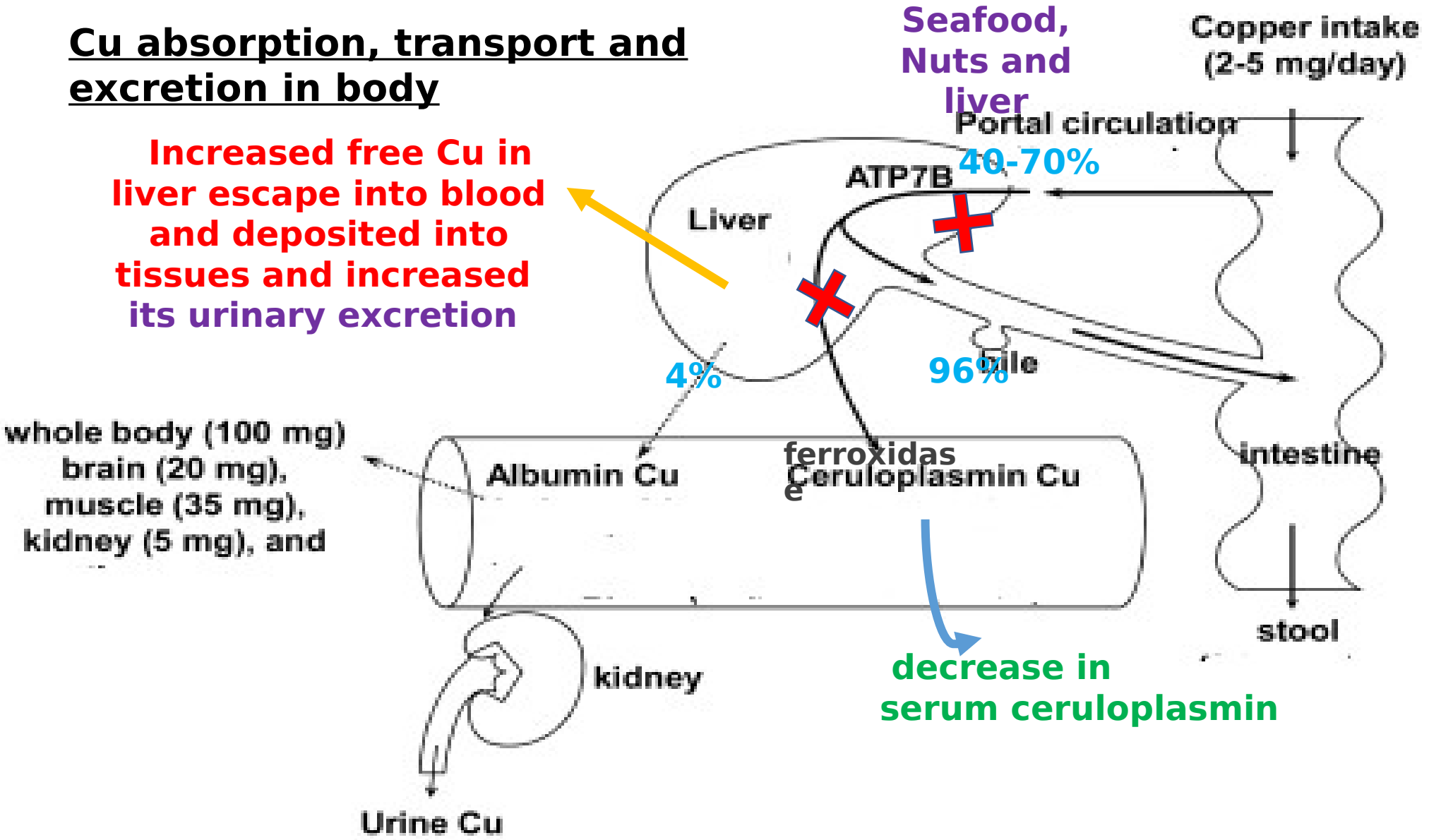
**Activity of many enzymes as:**

1. Superoxide Dismutase (SOD)
2. Lysayle oxidase
3. Cytochrome c oxidase
4. Monoamino oxidase
5. Ferroxidase
6. Tyrosinase
7. Dopamine b-hydroxylase
8. Peptidyl-

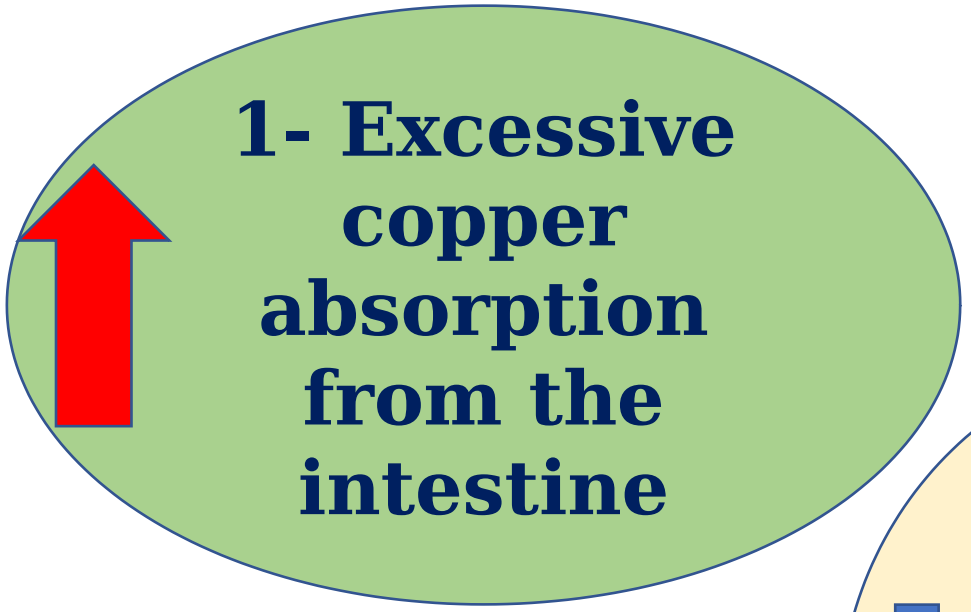
# Biochemical basis of Wilson's:

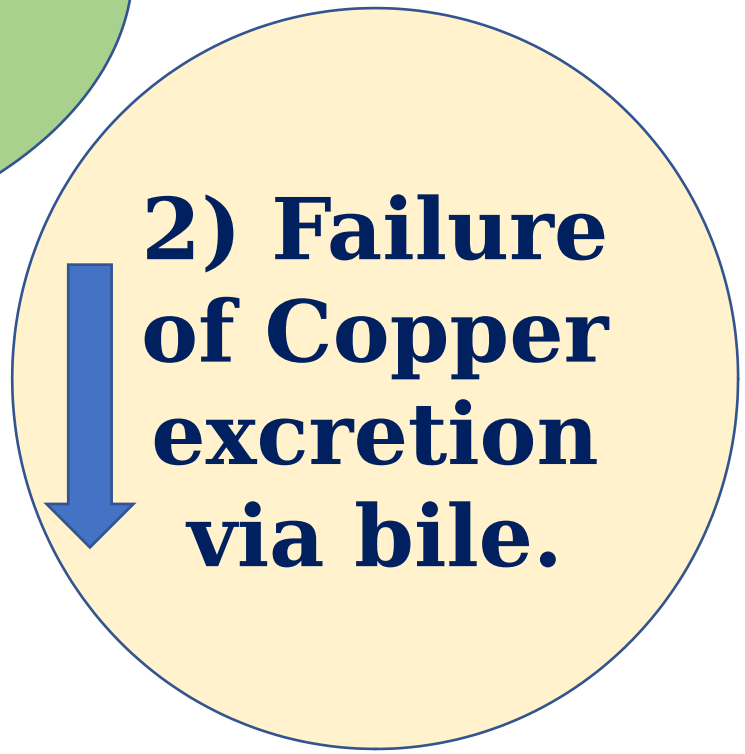
**It is a genetic disease (autosomal recessive disorder), due to mutation of ATP7B gene encodending membrane bound copper transporting ATPase**

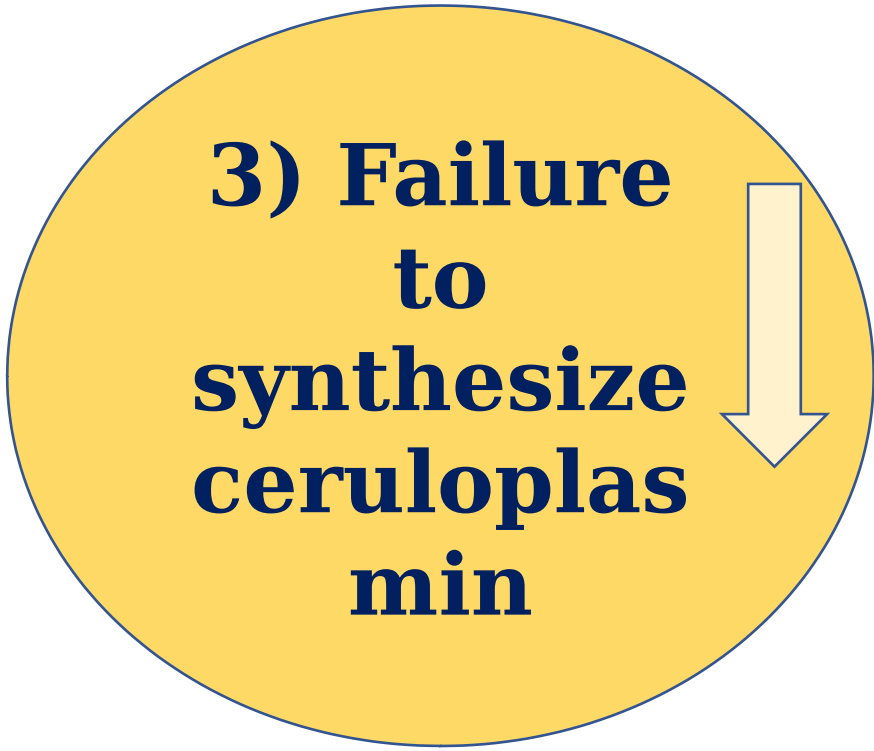
## Cu absorption, transport and excretion in body



# Biochemical basis of Wilson's:

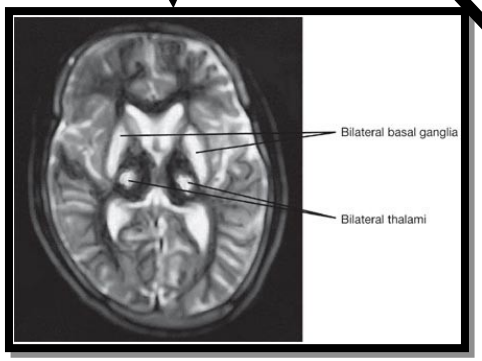


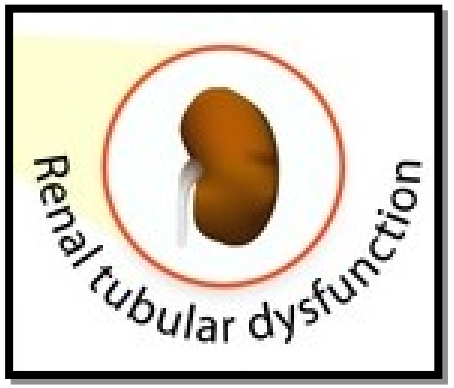



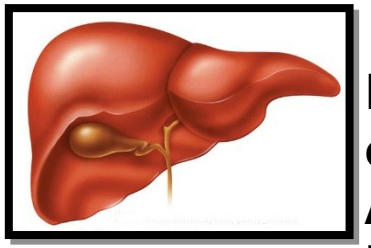
# Tissues where excess Cu deposit

**Dark, brown-colored rings around iris Cu deposit in (Descemet's membrane)**




**basal ganglia: Tremors, slurred speech change in behavior and Hyperintensities in MRI**



**Liver enlarged And may become cirrhotic**

# Laboratory diagnosis

**Ceruloplasmin level< 20 mg/day**
**Urinary copper excretion rate >100mg/day**
**Free copper level > 3.9 ug/dl (N: 8-12ug/dl)**
**Liver biopsy : CU levels >250 mg of dry weight**

**What is the mechanism of action of penicillamine in the treatment of this condition?**

- **chelates copper**
- **increase its excretion in urine.**

**NB : Zinc can block intestinal absorption of cu**

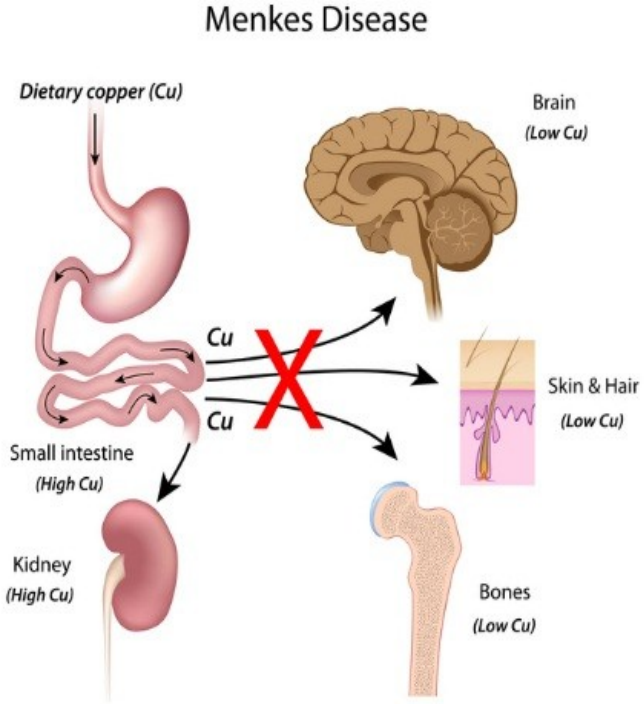
**Hypocupremia:**

**mutation ATP7A**
**gene encoding for protein that is important for regulating Cu levels and distributions of copper in the body cells**

**ndrome (Menk's kinky hai**

***Accumulation of Cu in intestine and kidney**

***Poor distribution of Cu in other body cells**

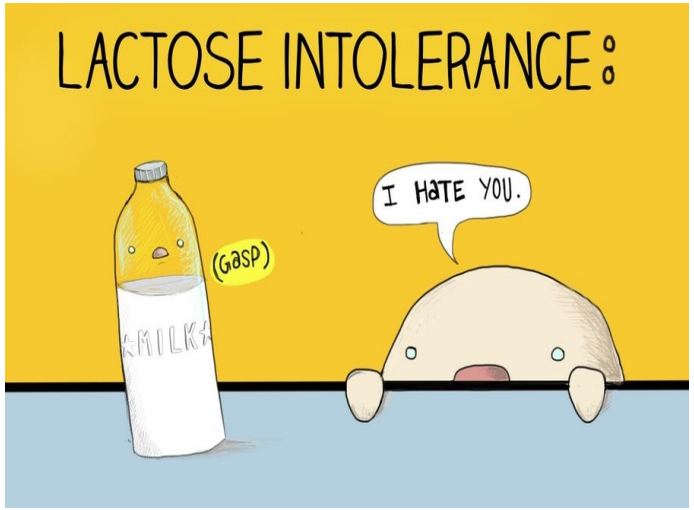


# Case


- **A 25-year-old woman presents with a 10-year history of intermittent diarrhea, abdominal pain, and flatulence.**

- **Recently her symptoms have worsened. She said that the change in symptoms may be related to her increased intake of milk over the last few months.**
- **Abdominal examination reveals a slightly distended abdomen.**

# What is your clinical impression?

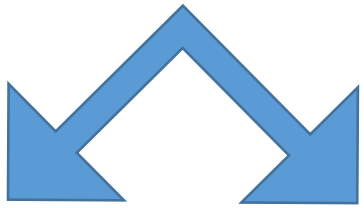



- Symptom:
- History
- Examination
- Bed test

- **Lactose intolerance due to Lactase deficiency**

# Clinical significance of Digestion

- Lactose intolerance is the inability to digest lactose due to the deficiency of Lactase enzyme.
- Causes



Congenital

Acquired during lifetime

Primary

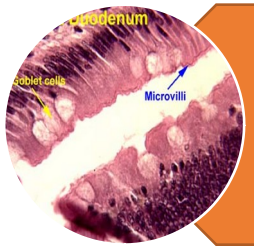
Secondary

# Congenital Lactose intolerance

- **It is a congenital disorder**
- **There is complete absence or deficiency of lactase enzyme.**
- **The child develops intolerance to lactose immediately after birth.**
- **It is diagnosed in early infancy.**
- **Milk feed precipitates symptoms.**

# Primary Lactase deficiency

- **Primary lactase deficiency develops over time**
- **There is no congenital absence of lactase but the deficiency is precipitated during adulthood.**
- **There is age-dependent loss of lactase activity  affect lactase gene expression  reduced amount of enzyme**
- **It is very common in Asian population.**
- **There is intolerance to milk + dairy products.**

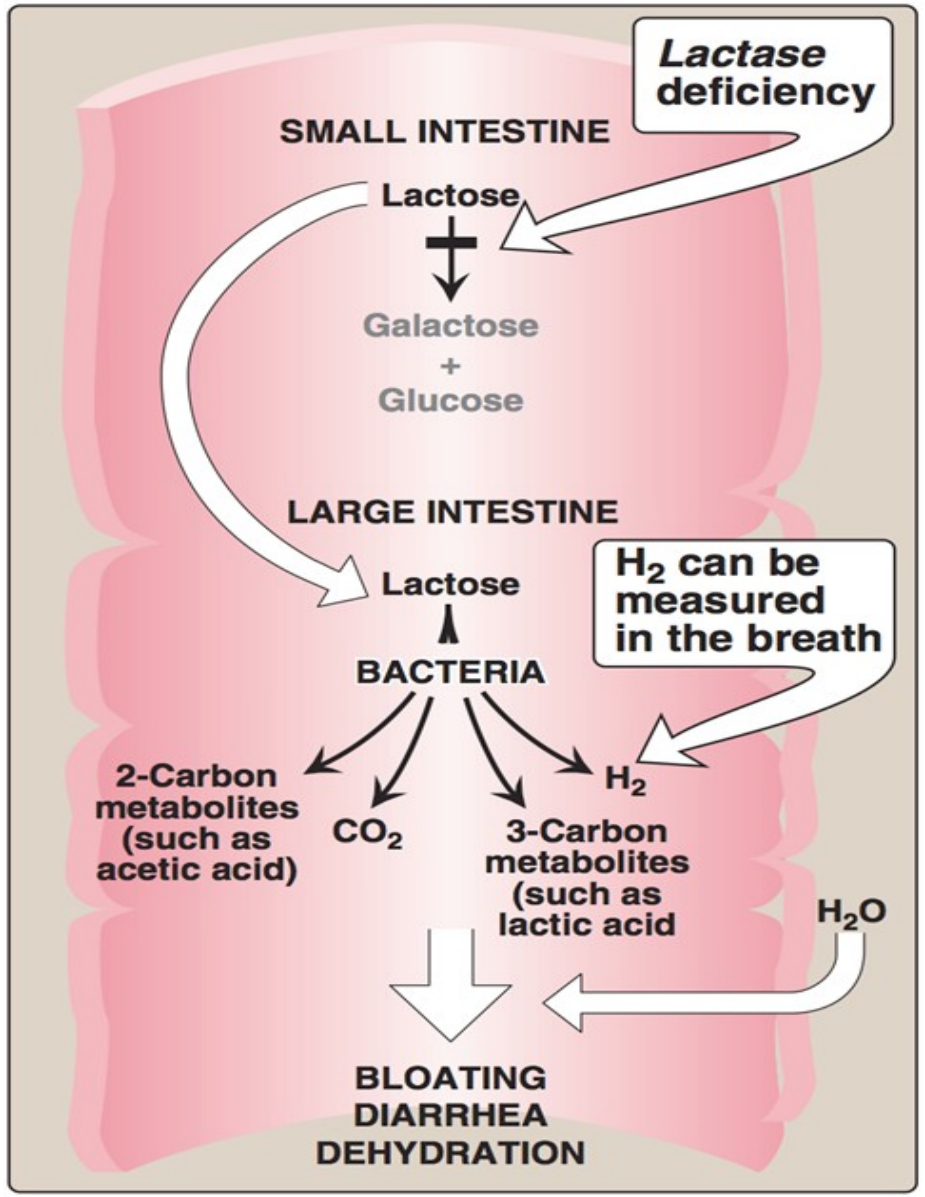



# Secondary lactase deficiency

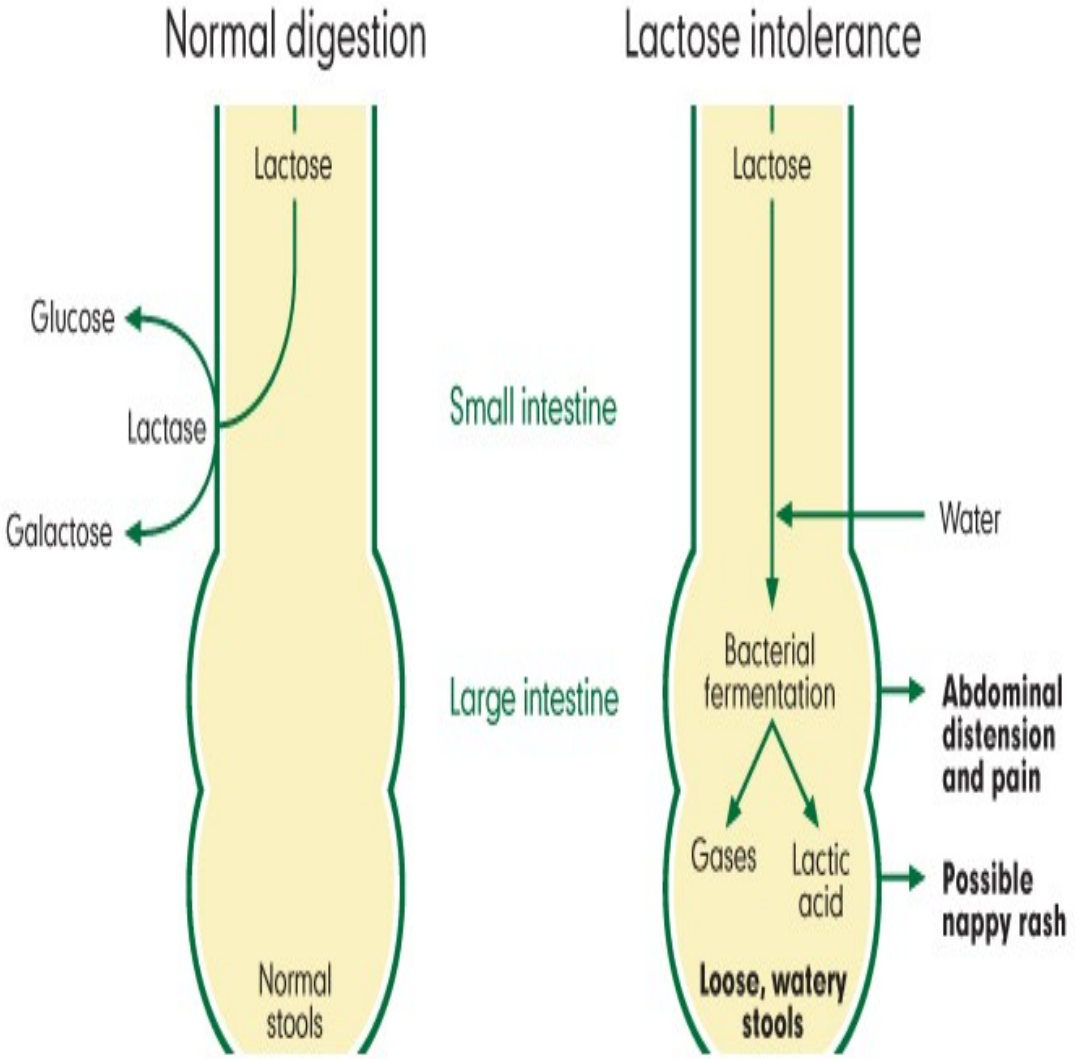
- This occurs because of mucosal damage or from medications resulting from certain **gastrointestinal diseases**, including exposure to **intestinal parasites** or **rotavirus.**

- Another form of temporary lactose intolerance is lactose overload is secondary to excess NSAID (non steroidal anti-inflammatory drug ) use or **chemotherapy**.

# Lactose intolerance




Symptoms of lactose intolerance



# Biochemical basis of lactose intolerance

**Lactose intolerance is a problem that results from an absence of lactase in the brush border of the small intestine.**

**Lactase is responsible for breaking down lactose into glucose and galactose, which are absorbed.**

**The undigested and unabsorbed lactose increases the osmotic gradient of the luminal contents, preventing the absorption of water.**

**The increased retention of fluid results in the symptoms of diarrhea with its abdominal distention and cramping.**

**The bacteria in the colon ferment the lactose into a variety of gases, leading to increased flatulence**

# Diagnosis

- *The commonly used tests are : -*
- **Hydrogen Breath Test**
- **Stool Acidity Test**
- **Mucosal biopsy** confirms the diagnosis.


# Management of lactose intolerance

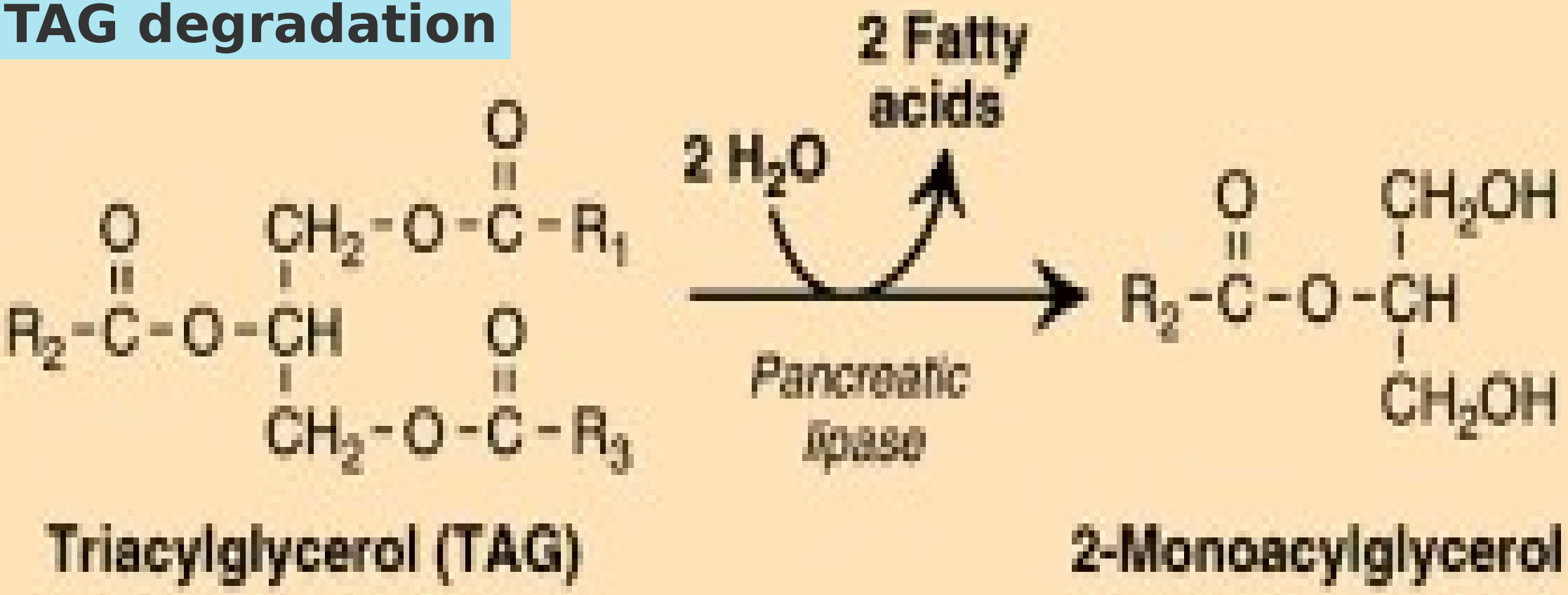
- Avoidance of dairy products.
- **Lactose-free, lactose-reduced milk**, Soy **milk** and other products may be recommended.
- **Lactase enzyme** drops or tablets(Yeast tablets) can also be consumed.
- Consume yogurts , some cheeses (**Bacterial action and processing decrease the lactose content)** ,
- Green vegetables (broccoli) (for Ca++ intake)

# CASE

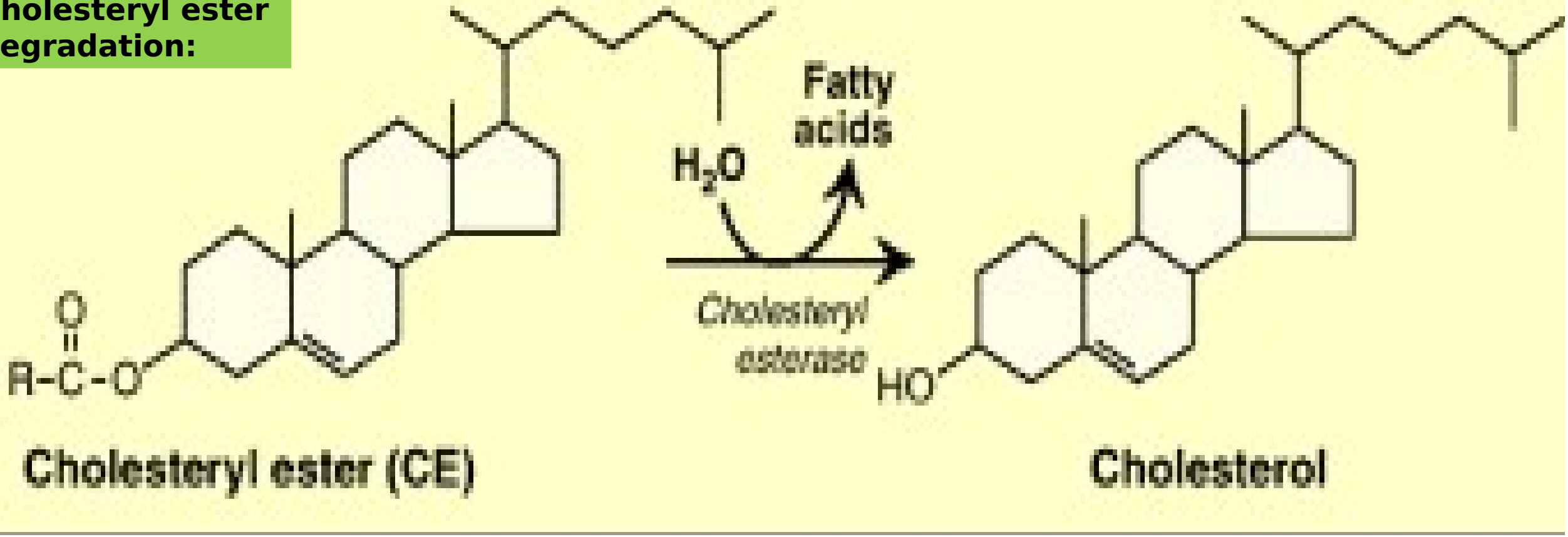
A 15 year old girl presents to the physician's office with a three year history of intermittent **diarrhea**.
She is thin and small for age but not cachectic. A stool examination is **negative for blood**. The 72-hour fecal fat study shows a **moderate increase in fat content**.
A CBC shows a mild anemia. Her iron studies indicate the presence of iron deficiency.
Her small size, the **steatorrhea and the iron deficiency all suggest the possibility of some type of GI malabsorption condition**.

# *List the pancreatic enzymes Used for Degradation of dietary lipids.*

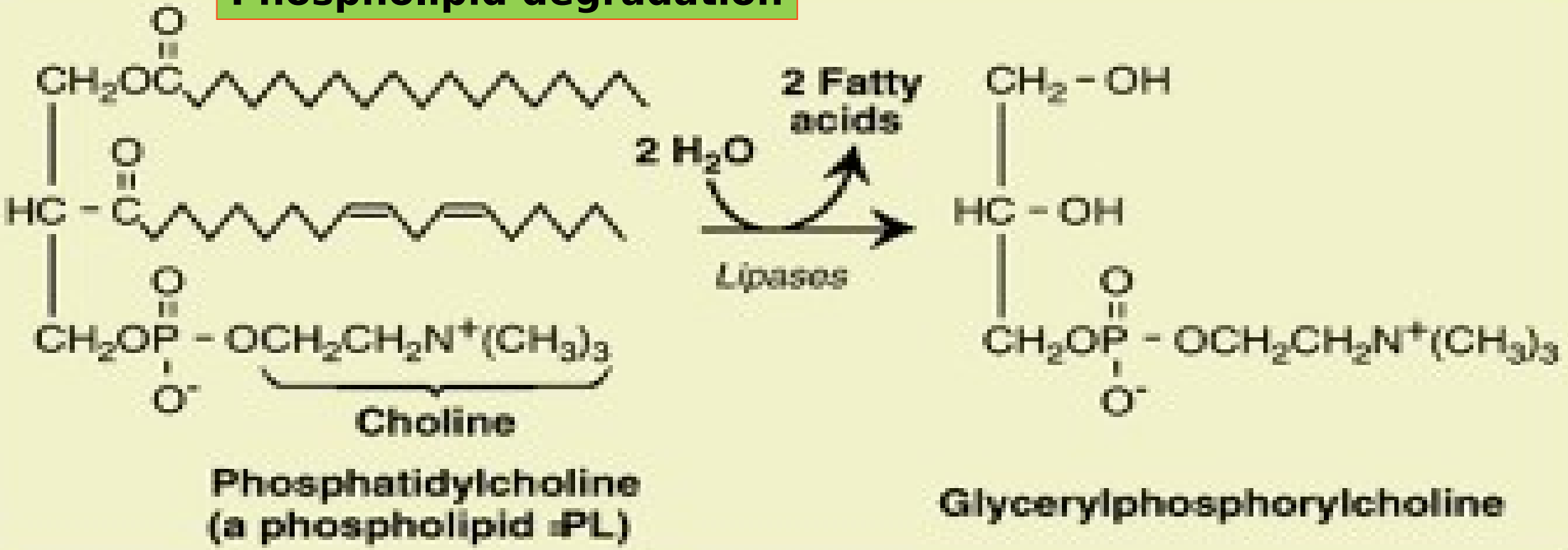
## TAG degradation



**Cholesteryl ester degradation:**



## Phospholipid degradation



# Name the phases of protein digestion and discuss

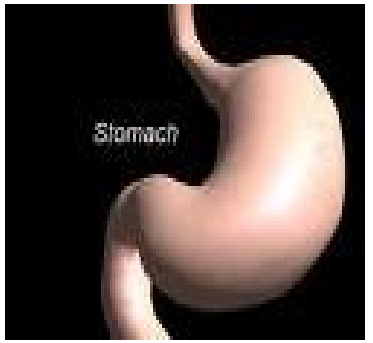
1. **Gastric phase**

- **2. Pancreatic phase**

- **3. Intestinal phase**

# 1-Gastric phase

: **Gastrin stimulates** release of **HCL** from **parietal cells**
**pepsin** from **chief cells**




**Pepsin + HCL**

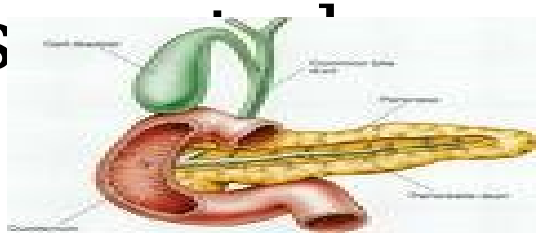
- **proteins**

**smaller polypeptides + a.as**

**Pepsin is an endopeptidase, hydrolyses the peptide l**
**adjacent to acidic or aromatic amino acids.**

# 2- Pancreatic phase

* The proteolytic action of pancreatic secretion is due to action of *endopeptidases* (which s[illegible] **zymogens)** and *carboxypeptidase.*



- **A) <u>Endopeptidases</u>** act in the **middle** of a polypeptide chain

**Trypsinogen, chymotrypsinogen, proelastase**

**Trypsin, chymotrypsin, elastase**

**Polypeptides** → **Tri/dipeptides + amino acids**

# 2- Pancreatic phase

**1- Trypsin hydrolyses the peptide bonds containing the carboxylic group of basic amino acids (arginine).**

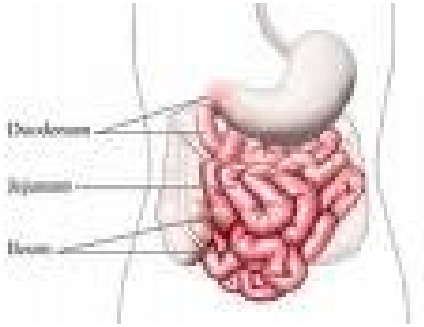
**2- Chymotrypsin** attacks the peptide bonds formed by **carboxylic group of aromatic amino acids, e.g. (phenyl alanine).**

**3- Elastase** hydrolyzes the peptide bonds next to some **non-polar amino acids** such as **(glycine & alanine).**

# 2- Pancreatic phase

- **B) Carboxy-peptidase**
- secreted as inactive pro-carboxypeptidase
- activated by trypsin.
- It acts on the **C-terminal peptide** bond.
- It is an **Exopeptidase.**

# 3- Intestinal phase



## *Amino-peptidases

are **exopeptidases** separating

the **N - terminal amino acids** in oligopeptides.


## *Tri-peptidases & Di-peptidases

act on tri- & dipeptides

producing **free amino acids**.

# Case

- A 46 y-old woman presented for follow up examination. Her medical history is notable only for diabetes and borderline hypertension?? .She has a family history of Diabetes and HTN . The patient has not followed the recommended life style changes nor regular treatment . On Examination, her Bl.P 140/93 and her BMI is 35 kg/m2 . A fasting plasma glucose level is 250mg/dl .
- Lab date revealed
- AsT : 50Iu/ml (normal 10-40)
- ALT : 60 Iu/ml (normal 5-40)
  - TC = 362mg/dl TAG = 152 mg/dl
  - HDL = 36 mg/dl LDL = 266 mg/dl

- **What is most likely diagnosis ?**
- **What is the possible complication if not treated?**
- **What is the next step?**

# What is most likely diagnosis ?

# fatty liver

## Causes of fatty liver

**Metabolic**

**Nutritional**

**Drugs and toxins**

## The following mechanisms could be responsible for the occurrence of fatty liver:

**1.↑ mobilization of FA** (from diet or from adipose tissueas in starvation or DM) → elevated plasma FFA and their hepatic uptake →activated to acyl CoA =increased TAG synthesis.

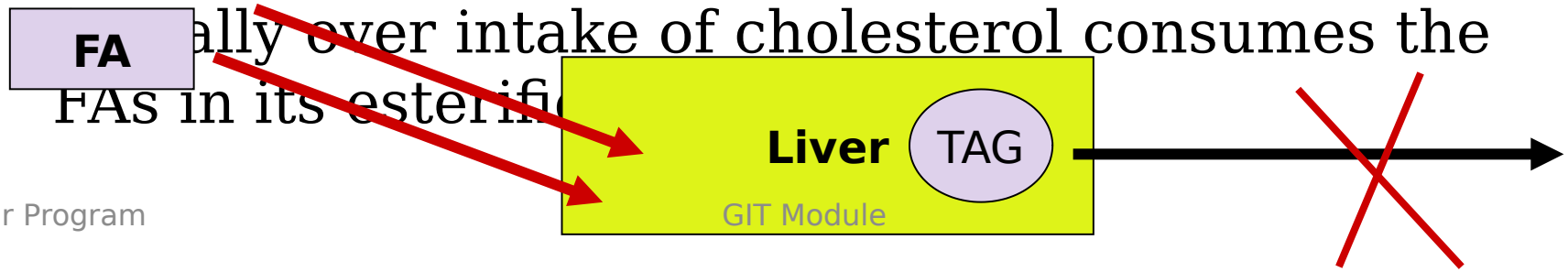
2. **Failure of liver to synthesize VLDL**, could be due to:

- failure to synthesize apoB100
- failure to release VLDL.
- failure to synthesize phospholipids due to :

✓ deficiency of lipotropic factors

✓ ↓ level of unsat FA that esterify position 2 of PL

ally over intake of cholesterol consumes the FAs in its esterifi



# What is the possible complication if not treated?

The accumulated TAG results in liver enlargement , fibrosis and cirrhosis with impaired liver function

# What is the next step?

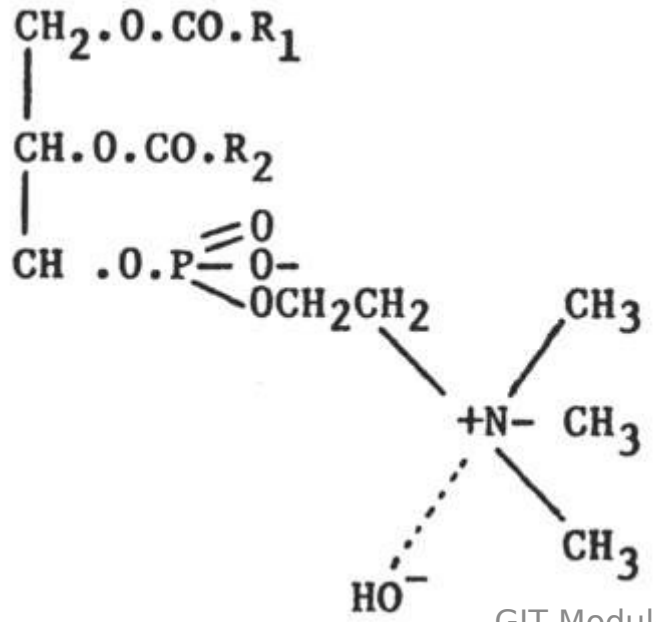
- **Follow the recommended life style changes (healthy diet with regular exercise)**
- **Regular treatment and controlled blood glucose level.**
- **Lipotropic factors**

# Lipotropic Factors

- These are substances that protect against and cure fatty liver.
- They include mainly the substances **essential for synthesis of phospholipids** which are easily t iable to deposit

# Lipotropic substances are:

1. **Choline, inositol, serine and ethanolamine** (constituents of PL)
2. **Methionine and betaine** ( methyl donors for choline)
3. **Casein** ( rich in methionine).




***phosphatidyl choline***

# Lipotropic substances; con.

4. **Estrogen** inhibits HMG-CoA reductase (the key enzyme of FA synthesis).
5. **Essential FA**, eg, linoleic acid (Unsat.FA enter in PL synthesis)
6. **Vits. B12 , folic acid, pantothenic acid** (help transmethylation reactions for choline PL synthesis)
7. **Vit. E & selenium**: protect against FFA oxidation
8. **pyridoxine (B6)**: essential cofactors for enzymes involved in various metabolic


Thank you